

**MULTITRACE-4 NEONATAL- trace elements 4 injection, solution**  
**American Regent, Inc.**

*Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.*

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**MULTITRACE®-4 NEONATAL (TRACE ELEMENTS INJECTION 4, USP)**

FOR IV USE AFTER DILUTION

**Rx Only**

**DESCRIPTION**

**MULTITRACE® - 4 NEONATAL (TRACE ELEMENTS INJECTION 4, USP)** is a sterile, nonpyrogenic solution containing four trace elements for use as an additive for Total Parenteral Nutrition (TPN).

**Each mL provides:**

Zinc	1.5 mg
Copper	0.1 mg
Manganese	25 mcg
Chromium	0.85 mcg

**Each mL contains:**

Zinc Sulfate (Heptahydrate)	6.6 mg
Cupric Sulfate (Pentahydrate)	0.39 mg
Manganese Sulfate (Monohydrate)	77 mcg
Chromic Chloride (Hexahydrate)	4.36 mcg
Water for Injection	q.s

pH (range 2.3-2.7) may be adjusted with Sulfuric Acid and/or Sodium Hydroxide.

Zinc Sulfate is chemically designated  $ZnSO_4$ , a white crystalline compound freely soluble in water. Cupric Sulfate is chemically designated  $CuSO_4$ , a blue crystalline compound very soluble in water. Manganese Sulfate is chemically designated  $MnSO_4$ , a pale red, slightly efflorescent compound soluble in water. Chromic Chloride is chemically designated  $CrCl_3$ , a greenish compound, soluble in water.

**CLINICAL PHARMACOLOGY**

**ZINC** is an essential nutritional requirement that serves as a cofactor for more than 70 different enzymes including carbonic anhydrase, alkaline phosphatase, lactic dehydrogenase, and both RNA and DNA polymerase. Zinc facilitates wound healing, helps maintain normal skin hydration, and senses of taste and smell.

Zinc resides in muscle, bone, skin, kidney, liver, pancreas, retina, prostate, and particularly in the red and white blood cells. Zinc binds plasma albumin  $\alpha_2$ -macroglobulin, and some plasma amino acids including histidine, cysteine, threonine, glycine, and asparagine. Ingested zinc is excreted mainly in the stool (approximately 90%), and to a lesser extent in the urine and in perspiration. Providing zinc during TPN prevents development of the following deficiency symptoms: Parakeratosis, hypogeusia, anorexia, dysosmia, geophagia, hypogonadism, growth retardation and hepatosplenomegaly.

The initial manifestations of hypozincemia in TPN patients are diarrhea, apathy, and depression. At plasma levels below 20 mcg zinc/100 mL, dermatitis followed by alopecia has been reported for TPN

patients. Normal zinc plasma levels are  $100 \pm 12$  mcg/100 mL.

**COPPER** is an essential nutrient that serves as a cofactor for serum ceruloplasmin, an oxidase necessary for proper formation of the iron carrier protein, transferrin. Providing copper during TPN helps prevent development of the following deficiency symptoms: leukopenia, neutropenia, anemia, depressed ceruloplasmin levels, impaired transferrin formation and secondary iron deficiency.

Normal serum copper values range from 80 to 163 mcg/100 mL (mean, approximately 110 mcg/100 mL). The serum copper level at which deficiency symptoms appear is not precisely defined. The daily turnover of copper through ceruloplasmin is approximately 0.5 mg. Excretion of copper is through the bile (80%), directly through the intestinal wall (16%), and in urine (4%).

**MANGANESE** is an essential nutrient that serves as an activator for enzymes such as polysaccharide polymerase, liver arginase, cholinesterase, and pyruvate carboxylase.

Providing manganese during TPN prevents development of the following deficiency symptoms: nausea and vomiting, weight loss, dermatitis, and changes in growth and color of hair. Under conditions of minimal intake, 20 mcg manganese/day is retained. Manganese is bound to a specific transport protein, transmanganin, a  $\beta_1$ -globulin. Manganese is widely distributed but concentrates in the mitochondria-rich tissues such as brain, kidney, pancreas, and liver. Assay for manganese in whole blood results in concentrations ranging from 6 to 12 mcg manganese/liter. Excretion of manganese occurs mainly through the bile, but in the event of obstruction, ancillary excretion routes include pancreatic juice, or return to the lumen of duodenum, jejunum, or ileum. Urinary excretion of manganese is negligible.

Trivalent **CHROMIUM** is part of glucose tolerance factor, an activator of insulin-mediated reactions. Chromium helps to maintain normal glucose metabolism and peripheral nerve function. Providing chromium during TPN prevents development of the following deficiency symptoms: impaired glucose tolerance, ataxia, peripheral neuropathy, and a confusional state similar to mild/moderate hepatic encephalopathy.

Serum chromium is bound to transferrin (siderophilin) in the  $\beta$ -globulin fraction. Typical blood levels for chromium range from 1 to 5 mcg/liter, but blood levels are not considered a meaningful index of tissue stores. Administration of chromium supplements to chromium-deficient patients can result in normalization of the glucose tolerance curve from the diabetic-like curve typical of chromium deficiency. This response is viewed as a more meaningful indicator of chromium nutriture than serum chromium levels.

Excretion of chromium is via the kidneys, ranging from 3 to 50 mcg/day. Biliary excretion via the small intestine may be an ancillary route, but it is believed that only small amounts of chromium are excreted in this matter.

## INDICATIONS AND USAGE

**MULTITRACE® - 4 NEONATAL** is indicated for use as a supplement to intravenous solutions given for TPN. Administration of **MULTITRACE® - 4 NEONATAL** in TPN solutions helps to maintain plasma levels of zinc, copper, manganese, and chromium and to prevent depletion of endogenous stores of these trace elements and subsequent deficiency symptoms.

## CONTRAINDICATIONS

**MULTITRACE® - 4 NEONATAL** should not be given undiluted by direct injection into a peripheral vein because of the potential of infusion phlebitis.

## WARNINGS

**MULTITRACE® - 4 NEONATAL is a hypotonic solution which should be administered in admixtures only. Supplementation of TPN solutions with Neonatal Formula should be**

**immediately discontinued if toxicity symptoms due to any of the constituent trace elements in Neonatal Formula is observed in the patient.**

**This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.**

**Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.**

## **PRECAUTIONS**

1. Before administering **MULTITRACE® - 4 NEONATAL** in TPN solutions, the physician must assess the metabolic requirements of trace elements and disease state of the patient. Frequent determinations of serum levels of the four trace elements are suggested as a guideline for adjusting the dosage or completely omitting **MULTITRACE® - 4 NEONATAL**. ZINC is eliminated via the intestine and kidneys; COPPER and MANGANESE are eliminated via the bile; and CHROMIUM primarily via the kidneys. The possibility of their retention should be considered in patients with malfunctioning excretory routes of the respective trace elements.
2. Syringes equipped with aluminum needles or hubs should not be used, as the solution is acidic.

### ***Pregnancy***

#### **Teratogenic Effects**

Pregnancy Category C: Animal reproduction studies have not been conducted with **MULTITRACE® - 4 NEONATAL**. It is also not known whether Neonatal Formula can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Neonatal Formula should be given to a pregnant woman only if clearly needed.

## **ADVERSE REACTIONS**

The amounts of **ZINC, COPPER, MANGANESE, and CHROMIUM** in **MULTITRACE® - 4 NEONATAL** are very small and toxicity symptoms due to these trace elements at suggested dosage levels are considered unlikely to occur.

## **OVERDOSAGE**

Single intravenous doses of 1 to 2 mg zinc/kg body weight have been given to adult leukemia patients without toxic manifestations. However, acute toxicity was reported in an adult when 10 mg zinc was infused over a period of one hour on each of four consecutive days. Profuse sweating, decreased level of consciousness, blurred vision, tachycardia (140/min.), and marked hypothermia (94.2°F) on the fourth day were accompanied by a serum zinc concentration of 207 mcg/mL. Symptoms abated within three hours. Hyperamylasemia may be a sign of impending zinc overdosage; patients receiving an inadvertent overdose (25 mg zinc/liter of TPN solution, equivalent to 50 to 70 mg zinc/day) developed hyperamylasemia (557 to 1850 Klein units; normal: 130-310).

Death resulted from an overdose in which 1683 mg zinc was delivered intravenously over the course of 60 hours to a 72 year old patient. Symptoms of **ZINC** toxicity included hypotension (80/40 mm Hg), pulmonary edema, diarrhea, vomiting, jaundice, and oliguria, with a serum zinc level of 4184 mcg/100 mL. Calcium supplements may confer a protective effect against zinc toxicity.

**COPPER** toxicity can produce prostration, behavior change, diarrhea, progressive marasmus, hypotonia, photophobia and peripheral edema. Such symptoms have been reported with a serum copper level of 286 mcg/100 mL. D-penicillamine has been reported effective as an antidote.

**MANGANESE** toxicity in TPN patients has not been reported within the prescribed dosage.

Trivalent **CHROMIUM** administered intravenously to TPN patients has been shown to be nontoxic when given at dosage levels of up to 250 mcg/day for two consecutive weeks.

Reported toxic reactions to chromium include nausea, vomiting, ulcers and gastrointestinal tract, renal and hepatic damage, convulsions, and coma. The acute LD<sub>50</sub> for intravenous trivalent chromium was reported as 10 to 18 mg/kg.

## **DOSAGE AND ADMINISTRATION**

The suggested dosage ranges for the four trace elements in neonates and pediatric patients are:

**ZINC:** For full term infants and children up to 5 years of age, 100 mcg zinc/kg/day is recommended. For premature infants up to 3 kg in body weight, 300 mcg zinc/kg/day is suggested.

**COPPER:** For pediatric patients, the suggested additive dosage level is 20 mcg copper/kg/day.

**MANGANESE:** For pediatric patients, a dosage of 2 to 10 mcg manganese/kg/day is suggested.

**CHROMIUM:** For pediatric patients, the suggested additive dosage 0.14 to 0.20 mcg chromium/kg/day.

Periodic monitoring of plasma levels of Zinc, Copper, Manganese and Chromium is suggested as a guideline preparation.

Aseptic addition of **MULTITRACE® - 4 NEONATAL** to parenteral nutrition solutions under a laminar flow hood is recommended. The trace elements present in the **MULTITRACE® - 4 NEONATAL** are physically compatible with the electrolytes and vitamins usually present in parenteral nutrition formulations.

Do not directly mix ascorbic acid injection with copper or selenium containing parenteral products in the same syringe or vial, as this admixture may cause the formation of an insoluble precipitate.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

## **HOW SUPPLIED**

### **MULTITRACE® - 4 NEONATAL (TRACE ELEMENTS INJECTION 4, USP)**

NDC 0517-6202-25          2 mL Single Dose Vial          Packaged in boxes of 25

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (See USP Controlled Room Temperature).

**AMERICAN  
REGENT, INC.  
SHIRLEY, NY 11967**

IN6202  
Rev. 8/18

## **PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

Container

**NDC 0517-6202-25**

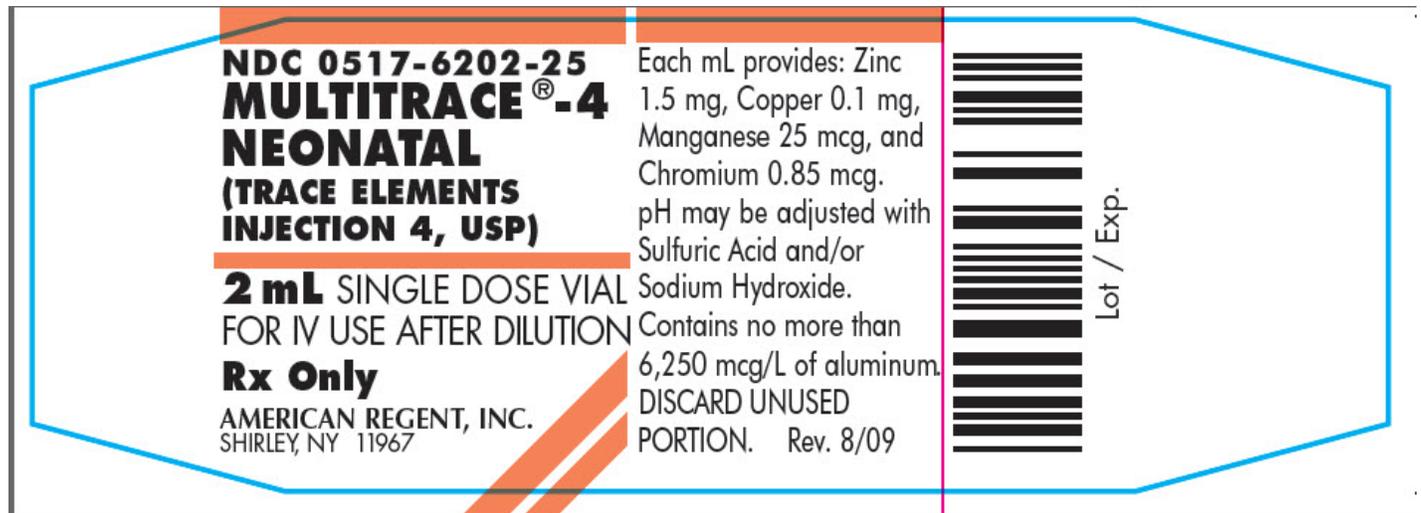
**MULTITRACE®-4 NEONATAL  
(TRACE ELEMENTS INJECTION 4, USP)**

**2 mL SINGLE DOSE VIAL**

**FOR IV USE AFTER DILUTION**

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SHIRLEY, NY 11967**



Carton

**MULTITRACE®-4 NEONATAL  
(TRACE ELEMENTS INJECTION 4, USP)**

**NDC 0517-6202-25**

**25 X 2 mL SINGLE DOSE VIALS**

**FOR IV USE AFTER DILUTION - PRESERVATIVE FREE**

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Each mL provides: Zinc 1.5 mg, Copper 0.1 mg, Manganese 25 mcg and Chromium 0.85 mcg. Each mL contains: Zinc Sulfate Heptahydrate) 6.6 mg, Cupric Sulfate (Pentahydrate) 0.39 mg, Manganese Sulfate (Monohydrate) 77 mcg, Chromic Chloride (Hexahydrate) 4.36 mcg, and Water for Injection q.s. pH may be adjusted with Sulfuric Acid and/or Sodium Hydroxide. Sterile, nonpyrogenic.

**WARNING: DISCARD UNUSED PORTION - USE ONLY IF SOLUTION IS CLEAR.**

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F); (See USP Controlled Room Temperature).

Directions for Use: See Package Insert.

**AMERICAN  
REGENT, INC.  
SHIRLEY, NY 11967**

Rev. 11/05

**MULTITRACE<sup>®</sup>-4**  
**NEONATAL**  
(TRACE ELEMENTS INJECTION 4, USP)

**NDC 0517-6202-25**  
**25 X 2 mL**  
**SINGLE DOSE VIALS**

**FOR IV USE AFTER DILUTION - PRESERVATIVE FREE**

**Rx Only**

Each mL provides: Zinc 1.5 mg, Copper 0.1 mg, Manganese 25 mcg and Chromium 0.85 mcg. Each mL contains: Zinc Sulfate (Heptahydrate) 6.6 mg, Cupric Sulfate (Pentahydrate) 0.39 mg, Manganese Sulfate (Monohydrate) 77 mcg, Chromic Chloride (Hexahydrate) 4.36 mcg, and Water for Injection q.s. pH may be adjusted with Sulfuric Acid and/or Sodium Hydroxide. Sterile, nonpyrogenic.

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Directions for Use: See Package Insert.

Rev. 11/05

Lot / Exp.

**AMERICAN  
REGENT, INC.**  
SHIRLEY, NY 11967



Serialization Label



# MULTITRACE-4 NEONATAL

trace elements 4 injection, solution

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:0517-6202
<b>Route of Administration</b>	INTRAVENOUS		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ZINC SULFATE HEPTAHYDRATE (UNII: N57J12K7WP) (ZINC CATION - UNII:13S1S8SF37)	ZINC CATION	6.6 mg in 1 mL
CUPRIC SULFATE (UNII: LRX7AJ16DT) (CUPRIC CATION - UNII:8CBV67279L)	CUPRIC CATION	0.39 mg in 1 mL
MANGANESE SULFATE (UNII: W00LYS4T26) (MANGANESE CATION (2+) - UNII:H6EP7W5457)	MANGANESE CATION (2+)	77 mg in 1 mL
CHROMIC CHLORIDE (UNII: KB1PCR9DMW) (CHROMIC CATION - UNII:X1N4508KF1)	CHROMIC CATION	4.36 ug in 1 mL

## Inactive Ingredients

Ingredient Name	Strength
SULFURIC ACID (UNII: O40UQP6WCF)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0K00R)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0517-6202-25	25 in 1 TRAY	09/30/1990	
1		2 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
UNAPPROVED DRUG OTHER		09/30/1990	

**Labeler** - American Regent, Inc. (002033710)

## Establishment

Name	Address	ID/FEI	Business Operations
American Regent, Inc.		002033710	ANALYSIS(0517-6202) , MANUFACTURE(0517-6202)